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Breaking News in Spinal Cord Injury Research

FDA Approved Phase I Clinical Trial of Human, Autologous Schwann Cell Transplantation in Patients with Spinal Cord Injuries

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On July 31, 2012, The Miami Project to Cure Paralysis at the University of Miami Miller School of Medicine received permission from the Food and Drug Administration (FDA) to begin a Phase I clinical trial to evaluate the safety of transplanting human autologous Schwann cells to treat patients with spinal cord injuries. This is the only FDA-approved cell therapy-based clinical trial for sub-acute spinal cord injury in the United States.

The Schwann cell clinical trial team, led by Dr. W. Dalton Dietrich, scientific director of the Miami Project, plans to transplant the patients' own Schwann cells into their injury sites in the hope of determining the safety of the procedure that will allow further trials to proceed. The team is composed of a multidisciplinary group of basic and clinical scientists, scientific staff, and regulatory personnel focused on advancing the trial. The team has been working diligently and carefully on this therapeutic concept for more than a quarter of a century. This trial, "when completed successfully, will lay the critical foundation for future cell-based therapies to target spinal cord injury," said Dr. Dietrich.

In this Phase I clinical trial, all procedures will be conducted in Miami at the University of Miami Hospital, Jackson Memorial Hospital, and The Miami Project to Cure Paralysis. The clinical trial will enroll eight participants with an acute thoracic spinal cord injury. Newly injured patients brought to the trauma center will have to meet the stringent criteria and agree to participate in further screening within 5 days of their injury. The participant will undergo a biopsy of a sensory nerve in one leg to obtain his or her own Schwann cells. The Schwann cells will be purified and expanded in culture for 3–5 weeks to generate a sufficient number of cells for transplantation. Schwann cells are expected to be surgically transplanted into the injury site at 26–40 days post-injury. After receiving the transplantation surgery, each participant will be followed intensely for 1 year, and their neurologic status, medical status, pain symptoms, and muscle spasticity will be evaluated. It is expected that the study may take at least 2–3 years from the time the first subject is enrolled until the final subject is 1 year post-transplantation.

The current FDA approved Phase I clinical trial is based on the groundbreaking work of Dr. Richard P. Bunge, the former scientific director of the Miami Project, and his long-term collaborator and wife, Dr. Mary Bartlett Bunge. The Bunge Laboratory pioneered methods for culturing myelin-forming glial cells, either alone or with nerve cells, enabling them to study the capabilities of isolated glial cells and interactions between glial cells and neurons. With the collaboration of Dr. Patrick Wood, another long-term scientific partner since 1970, they were able to grow neurons, Schwann cells, and fibroblasts separately and observed a number of important interactions that occur between these cells, not possible in an animal. It was Richard Bunge's dream that someday transplantation of human autologous

Schwann cells into the injured spinal cord might enhance recovery, the suggestion that he first espoused at a meeting at NIH in 1975. In a paper published in 1994, Dr. Bunge stated that “Since it is now possible to isolate Schwann cells both from neonatal and adult human peripheral nerve, their ability to promote regenerative efforts by many central neurons suggests a role for Schwann cell autografts in influencing central nervous system repair[1].”

Schwann cells, a major cellular component of peripheral nerve, were described by and named after the German anatomist, Theodore Schwann (1810–1882). Schwann cells are a unique cell type for cell-based transplantation after spinal cord injury[2,3,4,5,6]. They are successful in repair because they express a variety of factors that support the growth of central axons. They also express on their surface axonal growth-supporting cell adhesion molecules, and produce axonal growth-promoting substrates such as laminin and fibronectin. One of the principal advantages of Schwann cells over other cell types for transplantation into the injured spinal cord is that Schwann cells are able to myelinate regenerating central axons. Many other cell types promote axonal regeneration, but do not form myelin sheaths around the new axon sprouts. Schwann cells do so and thus facilitate signal conduction in the regenerated axons. One could anticipate that if myelination does not occur after regeneration and synapses do not form, the functioning of the new axons would be significantly impaired, possibly to a degree as seen in multiple sclerosis.

To employ Schwann cells for transplantation into the spinal cord, large numbers of cells are necessary in order to fill the cystic cavities that develop after injury. For that purpose, several methods have been developed including the one developed by Dr. Wood[7]. In 1991, the Bunge Laboratory, developed a method to isolate and obtain large, essentially pure populations of Schwann cells from the adult peripheral nerve[8]. Using this method, several millions of Schwann cells at a purity of 98% could be obtained within 10 weeks *in vitro*. In this study, the cultured Schwann cells were shown to retain their ability to myelinate and promote axonal regeneration *in vitro*. Using the same purification technique as developed for rat Schwann cells, the Bunge Laboratory also was able to obtain Schwann cells from human peripheral nerves[9]. This opened a new avenue for preparing large numbers of Schwann cells for autologous transplants for human application, which would minimize the risk of immunological rejection. Without a doubt, a faster generation of more cells would allow for more effective repair approaches. With these issues in mind, the Bunge Laboratory further improved the previously established method of harvesting human Schwann cells and used the mitogenic combination of heregulin and forskolin for 2 weeks prior to dissociation of the human nerve explants[10]. This approach significantly improved the Schwann cell yield, purity, and proliferation rate. With these improvements to generate more cells in time, potential obstacles for the use of human Schwann cells in the clinic for repair of the spinal cord have been overcome.

Over the past two decades, researchers in the Bunge Laboratory at the Miami Project tested extensively the efficacy and feasibility of Schwann cell transplantation, isolated from both rats and humans, in the repair of spinal cord injury using various spinal cord injury models, alone or in combination with other repair strategies[11,12,13,14,15,16,17,18,19,20,21,22,23,24]. These studies formed a strong scientific basis for the approved trial.

We congratulate the Miami Project scientists on receiving the FDA approval for this landmark Phase I clinical trial and wish them every success. Since spinal cord injury is a complex process that involves both primary and secondary pathological changes, it is likely that future success will be dependent on a combination of optimal strategies in which Schwann cell transplantation could play a fundamental role. This study, currently conducted by the Miami Project research team, is certainly an important step in the field. It opens a new era of cell-based therapy for patients with spinal cord injuries.

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Figures and Tables

Drs. Richard P. Bunge and Mary Bartlett Bunge